(Action, page 3.) The examiner provides no justification under the law that a "working example" must be present for enablement. Nor does the examiner indicate what he would require as a "working example." Therefore, the examiner's basis for the enablement rejection is not sufficient grounds for the rejection.

With regard to "specific guidance," guidance is presented on page 22 of the application about how to select suitable ungulate embryos from which ES cells are derived. On pages 23-26 of the specification, detailed steps are presented for initiating and maintaining ungulate embryo cultures, isolating ungulate ES cells, and maintaining ES cells in culture. The morphological features of ES cells and cultures are found on pages 14-15 of the specification.

Tips for isolating ES cells from pigs and sheep are presented on page 24, lines 11-25. Table 3 describes ES cell morphology of ungulates. Porcine and sheep ES colonies are described on pages 24-25. Determining the modal chromosome member to see if an ES culture is stable, is described on page 26 for pigs, cattle, sheep and goats. Guidance on how to maintain ES cells in culture is presented on pages 26-28 for pigs and sheep. Table 2, page 44, presents comparative methods of making ES cell lines in pig, cattle, sheep and goats.

Methods for producing chimeric ungulates from ES cells are given on pages 29-31, including methods to introduce genes by manipulation of the ES cells, and methods for identifying chimeras (pages 31-32).

Suitable first and second breeds of swine, goats, sheep and cattle and suitable markers for these species are presented on page 32. (See also Materials and Methods, in

particular the "Collection of Swine, Bovine, Ovine and Caprine Embryos and Isolation of ES-Like Cells," pp. 69-75).

The examiner doubts the assertion in the application that the claimed methods work for ungulates other than sheep. The declaration enclosed with this response from the inventor, Dr. Wheeler, attests that sheep ES cells were prepared following the protocols of the present specification.

Although it is true that there are some differences in embryonic development among ungulates, these differences are not shown by the examiner to affect response of the different ungulate species to the methods of the present invention for producing chimeras.

With regard to the Piedrahita et al. (A52) publication cited by the examiner, only potential swine stem cells were isolated. Piedrahita was unable to maintain "ES" cell lines or to demonstrate the isolated cells' pluripotency. Therefore, there is no evidence ES cells were produced. There was no assertion that ovine embryos produced ES cells. The methods disclosed by Piedrahita could not be described as "a method to produce embryonic stem cells," which implies substantial homogeneity and reproducibility, neither of which were demonstrated. Applicant maintains that ES cells were not produced by Piedrahita et al., therefore, the examiner's concern "that porcine and ovine embryos responded differently to the same treatments "(Action, page 3) is not relevant.

The examiner points to "differences" among species reported by Cruz et al. and by Bazer et al., but fails to mention similarities among ungulates described in these publications, e.g. "The pattern of development during cleavage is similar for all farm species studied" (see Table 8-2). Table 8-2 relates cattle, horse, sheep, and swine.

The need for undue experimentation is not a necessary consequence of differences among species. The same protocols described in detail in the specification, and admitted by the examiner to be "enabling for swine" (Action, page 3), may be applied to other ungulates.

Methods in the art to "validate" ES cells are in the specification as e.g. on page 10, as acknowledged in the Action, page 3. Therefore, those practicing the invention can readily determine whether or not they have produced ES cells by following the guidelines of the invention. Production of tumors in an immunocompromised mammal is another method.

The examiner mentions applicant's comments about species differences. Concerns in the application are about extrapolating from mice to ungulates (application, page 5, lines 4-8) that is, concerns about differences in embryonic development among biological (taxonomic) genera. Extrapolating from swine to other ungulates is extrapolating within a genus, therefore development should be more similar. Indeed, similarities among ungulates and differences between ungulates and rodents are discussed in the application on page 8, lines 26-35; page 9, lines 1-35; page 10, lines 1-5; page 22, lines 8-26.

Because ungulate embryological development is similar among the member species, and ES cells and chimeric pigs have been produced from pigs and, according to the application and Dr. Wheeler's declaration, ES cells have been produced from sheep, the production of chimeric ungulates other than swine should not require undue experimentation.

For the reasons stated, Applicant requests reconsideration of the claims rejected under 35 U.S.C. § 112. In addition, two new claims, 22 and 23 are presented for the examiner's consideration. These claims are the same as claims 1 and 15, except for

substitution of the word "swine" for "ungulates." If necessary for allowance, Applicant is willing to so amend the dependent claims also, without prejudice to prosecute ungulate claims in a continuing application. It is recognized that claim 23 could prompt a double-patenting objection from the examiner. A response to this general issue is contained in Section IV herein.

III. Claims 1, 2, 4-7 and 9 As Amended Are Not Anticipated by Kashiwazaki; Claims 8 and 10-13 As Amended are Not Obvious Over Kashiwazaki

Applicant disagrees that Kashiwazaki anticipates or makes obvious the claims captioned above. Kashiwazaki does not teach ES cells, but rather uses cells directly from the inner cell mass of an embryo that are not demonstrably ES cells. However, to move this application toward allowance, claims are amended to include the modifier "cultured" for ES cells, as suggested by the examiner. Claim 2, 4 -13 are dependent on amended claim 1, therefore incorporate its limitations and do not require separate amendments.

Applicant requests removal of the rejections based on Kashiwazaki.

IV. Double-Patenting Rejections

Claims 15-21 were rejected on the basis of obviousness – type double patenting over claims 1 and 2 U.S. Pat. No. 5,523,226 ('226). Claims 1-13 and 15-21 were rejected over 14-16 and 48-50 of U.S. Ser. No. 08/473,030 ('030).

As the examiner admits, claims 15-21, directed to making an ES cell, do not include the limitation of going through a SCID mouse as in claims 1 and 2 of '226 and also

relate the genus "ungulates." The examiner argues in the Action regarding section 112, that getting the invention to work in ungulates is unpredictable yet here states that claims to swine make claims to ungulates obvious and anticipated. Applicant respectfully requests reconsideration of this issue.

The examiner has not shown why removing the SCID limitation is obvious. Also, Applicant's invention is now known to apply to more than pigs (see citations to the application in Section II herein and Dr. Wheeler's declaration). However, if necessary for allowance, applicant will cancel claims 15-21 and new claim 23, reserving the right to prosecute them in a continuing application.

Because claims 1-13 and 15-21 are only provisionally rejected, terminal disclaimers may be worked out after allowance, if necessary.

V. Summary and Conclusions

Claim 3 was deemed free of the prior art and therefore is allowable pending resolution of the double-patenting rejection. Allowance of all other claims is also requested. If necessary, terminal disclaimers will be made after allowance.

Please contact applicant's representative below if there are any further questions or issues.

Please charge any fees necessitated by this submission to Deposit Account No. 23-1925.

Respectfully submitted,

Dated: September 16, 1997

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